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Ehrlich & Laquer



## On Continuous Treatment with Thalline, and its Action in Cases of Typhoid Fever.

BY

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Thalline — *i.e.*, Tetrahydroparachinanisol — synthetically produced by Skraupp, was first introduced into Therapeutics by Jaksch, who, in a great many cases, proved its eminently antipyretical action. Although this was corroborated by all succeeding authors—*viz.*, Alexander, Ewald, Landenberger, Mingazzini and Pisenti, Grocco, Guttman, &c.—as well as by ourselves, in all its essential details, Thalline, according to more recent publications, and especially the transactions of the last Congress for internal medicine, nevertheless could not gain any firm ground in practice.

In order to assign a reason for this fact, we must look partly to the transitory effect, showing itself in the speedy decrease of temperature; the short duration of the Apyrexia followed by a rapid increase of fever heat; and partly to the weighty circumstance of Hyperpyrexia and rigors occurring more or less frequently and simultaneously with the brisk rising of the temperature.

Antipyrine, on the other hand, had advantages such as gradual decrease of the fever, longer duration of this effect, and a more moderate rising of the temperature, in its favor, which readily explains its extensive use during the past year.

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\* After a lecture before the "Gesellschaft der Charité Aerzte," on November 19th, 1885.

We also, during the first period of our investigation with Thalline, met with unsatisfactory results when giving a single dose of four to five grains, as recommended by Jaksch, and were accordingly inclined to side with the unfavourable opinion towards it. Experience with larger doses ( $7\frac{1}{2}$  to  $10\frac{1}{2}$  grains), as given by Landenberger, in order to increase the duration of its action, also did not show the desired effect, the period of antipyrexia not being prolonged in a corresponding degree, while the secondary symptoms, such as profuse perspiration, rigors and dangerous collapse became considerably increased.

During these preliminary experiments, however, which extended over a long period of time, there were instances in which we obtained very satisfactory results (critical decrease of temperature in Pneumonia and Erysipelas), and it was this experience which induced us to continue in the adopted course, and to look for a more practical mode of administering the drug. In fact we obtained better and much more satisfactory results after emancipating ourselves from the single and more powerful doses, and adopting instead a continuous use of smaller quantities.

A few words will suffice to demonstrate the theoretical features of our proceeding. The two drugs in question—Antipyrine and Thalline—do not only differ with regard to their constituents, their action and their respective doses, but also show a diversity in the relations of absorption and elimination. In order properly to estimate the value of the latter points, the simplest way is to fix the time in which, after being administered, the drug becomes apparent in the different secretions and particularly in the urine. According to statements by Jaksch, the characteristic reaction of Perchloride of Iron may be discovered, half an hour to one hour after giving small doses of Thalline, whilst the larger doses of Antipyrine on the other hand require fully three hours for its production (Marigliano).

Furthermore taking into account that according to our own observations, as soon as 10 to 15 minutes after internally administering Thalline, profuse sweating may occur as the first symptom of its being sufficiently absorbed, it is to be inferred, that Thalline constitutes a therapeutic agent absorbed

by the stomach and eliminated by the kidneys with excessive rapidity. Its prompt action is consequently readily accounted for by its speedy absorption, thus furnishing the tissues of the organism with the quantity of Thalline necessary for producing Apyrexia in almost as short a time as if administered by subcutaneous injection. The rapid decrease of the temperature is in conformity with the absorption, while the short duration of the Apyrexia and the steep rising of the fever curve correspond to the swiftness with which the organism tries to rid itself of the surplus of the Thalline—small remnants only being left.

In contradistinction to this the slower decrease and increase of temperature after the use of Antipyrine, (shewing itself in an undulating incline of the curve, together with the protracted duration of the whole process), may be accounted for in an analogous manner, by a more difficult absorbability and a more tedious elimination. It thus became evident that the comparison of both drugs by the same mode of investigation, was utterly inadmissible, and we were consequently under the necessity of searching for another manner of administering Thalline.

It appeared to us as the most rational proceeding to substitute for the single large dose, smaller quantities, acting in a cumulative manner and being administered frequently during short intervals, in order artificially to protract the act of absorption and thus to weaken the brisk action of the drug. We found, that in following such a course, we attained the full antipyretic effects of large doses, obviating at the same time as completely as possible the disagreeable symptoms resulting therefrom. Besides it thus becomes possible to keep the organism under the continuous influence of Thalline in a most gentle manner for days and even weeks, at the same time administering not inconsiderable quantities of the drug (15, 30, 45 grs. per day). This manner of giving the medicine may therefore be considered highly rational and especially suitable in cases demanding information respecting specific actions.

In order to get a proper insight into the action of Thalline we thought it expedient to restrict our observations to one

specific class of diseases, selecting, as the basis of former experience, typhoid fever, as the most appropriate object for investigation.

Before however proceeding to the examination of the several cases, we should like in a few words to state the principles by which we were guided.

The treatment was adopted only in cases admitting the Diagnosis of Typhoid fever with all possible certainty, light and abortive cases being excluded from observation, in order not to preoccupy our judgment. We have in our experiments made use almost exclusively of *Thallinum tartaricum*, beginning mostly with a solution of one per cent. mixed with a little sugar and alcohol, from which with the aid of a measured glass the necessary quantity was administered every hour during day-time, and every two hours during the night. Later on the patients turning against the medicine so frequently given, on account of its disagreeable taste, it was considered advisable to dispense the quantity required in each individual case in the form of pills, taken hourly and every two hours during the night. In acting thus we observed in our patients not only the antipyretic effect, but also in most cases a favorable influence on the general system and in particular on the sensorial function. Temporary sweating occurred in the majority of cases, without however reaching a climax cumbersome to the patient. Collapse even after large diurnal doses and prolonged administration was totally absent. Rigors and shivering were observed only exceptionally and merely in cases where the selected single doses were wrongly estimated—*i.e.*, too large. Symptoms of irritation on the part of the central nervous system, of the kidneys, &c., were constantly absent, and the digestion in no way disturbed by the *Thalline*. In some cases vomiting occurred, but only after administering the watery solution, and evidently due to occasional nauseousness; its re-occurrence being prevented by the use of the pills. Skin affections were never met with, which deserves special mention, as it clearly demonstrates the existence of important and fundamental differences between *Antipyrine* and *Thalline*.

We now append the respective cases:—

1. Heede, baker's apprentice, aged 18, admitted on

July 17th, 1885. Diagnosis: Typhoid Fever (6th day); spleen greatly enlarged, Roseola, strong Diazoreaction, Diarrhœa, Typhoid tongue after four days' treatment with Thalline. Apyrexia on the eleventh day. During convalescence occasional nocturnal increase of temperature to 100.3°F. Enlargement of spleen and Diazoreaction persist during the first days after Apyrexia.

Scale of Temperature from July 17th (6th day):

2 p.m., 102.7°F  
4 „ 103.1  
6 „ 102.7  
8 „ 102

July 18th (7th day).

8 a.m. 101.3°F  
9 „ 101.1  
10 „ 100.9  
11 „ 100.2  
12 „ 98.9  
1 p.m. 100.9  
2 „ 101.6  
3 „ 101.5  
4 „ 100.7  
5 „ 101.1  
6 „ 101.3  
7 „ 102.6  
8 „ 102.7

July 19th (8th day).

8 a.m. 99°F  
9 „ 97.5  
10 „ 98  
11 „ 99  
12 „ 99  
1 p.m. 98.9  
2 „ 100  
3 „ 102  
4 „ 100.3  
5 „ 100.3  
6 „ 100.3  
7 „ 101.3  
8 „ 101.3

July 20th (9th day).

8 a.m. 99°F  
9 „ 99  
10 „ 96.8  
11 „ 97.8  
12 „ 98.2  
1 p.m. 98.6  
2 „ 99  
3 „ 100.9  
4 „ 100.3  
5 „ 101.5  
6 „ 101.6  
7 „ 100.7  
8 „ 100.9

From 9.30 a.m. till 11 a.m.  
 $\frac{3}{4}$  gr. Thalline, from  
11 a.m. till 8 p.m.,  $\frac{1}{4}$  gr.  
every half-hour; at  
2 and 4 p.m., perspira-  
tion, no shivering.

From 8.30 a.m. till 8 p.m.,  
 $\frac{1}{2}$  gr. Thalline every  
half-hour; no shiver-  
ing, at 2 p.m. per-  
spiration.

At 9 a.m. perspira-  
tion; from 8 a.m.  
till 8 p.m.  $\frac{1}{4}$  gr.  
Thalline every half-  
hour, no shivering.

July 21st (10th day).

8 a.m. 98.9  
9 „ 98.8  
10 „ 96.1  
11 „ 96.3  
12 „ 97.3  
1 p.m. 97.8  
2 „ 98.8  
3 „ 99.4  
4 „ 100.9  
5 „ 101.5  
6 „ 100.9  
7 „ 100.9  
8 „ 99.6

Same medicine as on the day before  
No shivering.

July 22nd (11th day).

8 a.m. 98.4  
9 „ 97  
10 „ 96.6  
11 „ 97  
12 „ 97  
1 p.m. 97.8  
2 „ 99.2  
3 „ 98.2  
4 „ 97.8  
5 „ 99.8  
6 „ 100.5  
7 „ 101.5  
8 „ 100.3

From 8 a.m. till 8 p.m.,  $\frac{1}{4}$  gr. of  
Thalline every half-hour. No  
shivering.

July 23rd (12th day).

8 a.m. 98.6  
9 „ 97.5  
10 „ 96.8  
11 „ 96.3  
12 „ 97.1  
1 p.m. 95.4  
2 „ 97.8  
3 „ 98.2  
4 „ 98.4  
5 „ 100.2  
6 „ 99.4  
7 „ 100  
8 „ 98.2

13th day. 14th day 15th day. 16th day.  
98.9 97.7 97.7 97.7

From July 23rd constantly normal  
temperature.

From 8 a.m. till 8  
p.m.,  $\frac{1}{4}$  gr. every  
half-hour; no  
sweating; no  
shivering.

2. Michaelis, aged 42, distiller (drunkard), admitted on September 4th. Diagnosis: Typhoid fever, 5th day; typhoid motions, Diazoreaction, Bronchitis, no Roseola. Patient was entirely free from fever on the tenth day, after 3 days treatment with Thalline. The drug on this day was stopped, as he refused to take it any longer. During the next seven days there was irregular and not unimportant increase of temperature (reaching 102.2° F.). No relapse. Good results.

		September.							
		4 5th day.	5 6th day.	6 7th day.	7 8th day.	8 9th day.	9 10th day.	10 11th day.	11 12th day.
8	a.m.	—	100.9	101.5	100.7	100	99.2	99.6	100.5
10	"	—	101.5	99	98.4	99.8	99.4	97.3	98
12	"	—	102.9	101.3	98.2	100.2	99.8	98.2	98.8
2	p.m.	—	102.4	100	100.2	101.1	99	101.5	100.3
4	"	—	102.6	102	100.2	100.9	99.4	100.3	100
6	"	100.7	103.1	101.3	102	102.2	98.9	102.2	100
8	"	103.1	104.2	101.3	102.7	102	99.4	99	100
		from 8 a.m. till 8 p.m. every hour 1½ grs. of Thal-line.							
		every hour 1½ grs. of Thal-line. At 6 p.m. vomit- ing. During the night 2 grs. every 2 hours.							
		every hour 1½ grs. of Thal-line. At 1.30 vomit- ing. 5 p.m. 1½ grs. every hour.							
		Thal-line discontinued every hour of the vomit- ing. From were ejected from the mouth. During the night 1½ grs. every 2 hours.							

3. Malucke, labourer, aged 17, admitted on May 29th. Typhoid fever, case of moderate intensity. 6th day, enlarged spleen, Roseola, moderate sensorial affection, retention of urine, strong Diazoreaction. From the 7th day single doses of Thal-line of 4 to 10 grs., mostly once daily; on 13th day, Apyrexia. Remarkable effect of the midday dose on the 13th day, Diazoreaction noticeable on one day after Apyrexia.

29th May (6th day.)

2 p.m. 103.1 °F.

4 " 103.1

6 " 103.5

8 " 103.1

31st May (8th day.)

8 a.m. 99.8 °F.

10 " 102.6 — 5 grs. Thall.

12 " 100.3

2 p.m. 98.9

4 " 98.9

6 " 99.4

8 " 101.5

## June 2nd (10th day)

8 a.m.	99·2°F.
10 "	100·7
11 "	98·8
12 "	98
1 p.m.	97·3
2 "	98·6
3 "	99
4 "	101·6
6 "	101·5
7 "	103·3
8 "	104

At 10 a.m. 6 grs of Thalline,  
4 minutes afterwards  
sweating. At 4 p.m.  
4 grs. of Thalline.

## June 3rd (11th day)

8 a.m.	97·7°F.
10 "	100·2
11 "	98·6
12 "	96·3
1 p.m.	95·2
2 "	96·4
3 "	99·2
4 "	101·1
5 "	103·1
6 "	103·5
7 "	103·3
8 "	103·1

At 10 a.m. 10 grs. of Thalline.

## June 4th (12th day).

8 a.m.	98·6°F.
10 "	98·6
11 "	98·2
12 "	98·6
1 p.m.	100
2 "	98·2
3 "	95·5
4 "	95·9
5 "	96·8
6 "	98·6
7 "	99·4
8 "	103·1

At 1 p.m. 8 grs. of  
Thalline.

## June 5th (13th day).

8 a.m.	97·1°F.
10 "	97·1
12 "	98·9
2 p.m.	99·2
4 "	96·8
6 "	97·3
8 "	99·4

At 2 p.m. 8 grs. of  
Thalline.

On the succeeding days normal temperature.

4. G a s t, apprentice, aged 16, admitted on August 31st, Typhoid fever, 8th day; Tumour of spleen, Roseola, strong Diazoreaction, Typhoid motion, Bronchitis, and Hypostasis on the right side. After 5 days' treatment, Apyrexia on the 14th day; Diazoreaction for 2 days longer. Good results.

August		September						
	31 8th day.	1 9th day.	2 10th day.	3 11th day.	4 12th day.	5 13th day.	6 14th day.	7 15th day.
6 a.m.	—	—	101·1·F	—	—	—	—	—
7 "	—	—	100	—	—	—	—	—
8 "	—	100·5	99·6	100·5	101·5	101·8	100	100·9
9 "	—	—	100	99·6	100·7	102·4	—	—
10 "	—	100·2	100	100·5	101·3	101·6	101·1	99·8
11 "	—	—	102	100·9	103·1	102·9	—	—
12 "	—	100·2	101·5	102·2	104	103·3	99·8	99
1 p.m.	—	100·7	101·3	103·1	102·6	102	—	—
2 "	—	101·6	103·8	103·5	100·7	101·3	98·2	97·5
3 "	—	102	102	103·3	100·5	102·7	—	—
4 "	102·4	103·5	102·2	101·6	100·5	102·9	98·4	98
5 "	—	102·6	102·9	99·6	101·5	100·9	—	—
6 "	103·1	102·2	102·7	102·6	102·2	101·1	98	99·2
7 "	—	102·4	102	101·6	102·6	100·2	—	—
8 "	103·1	102·4	100·9	101·6	101·1	99·2	97·8	98·9
		from 8 a.m. every hour 1 gr. of Thal- line ; from 9.30 p.m. till 5.30 a.m. 1½ grs. of Thal- line every 2 hours.	from 7.30 a.m. every hour 1 gr. of Thal- line ; from 9.30 p.m. as the day before.	from 8 a.m. till 2 p.m. 1 gr. of Thal- line every hour ; from 2 p.m. till 8 p.m. 1½ grs. every hour ; during the night as 1½ grs. every 2 hours.	from 8 a.m. till 11 a.m. 1½ grs. of Thal- line every hour ; from 11 a.m. till 8 p.m. 1½ grs. of Thal- line ; during the night as before.	from 8 a.m. till 10 a.m. 1½ grs. of Thal- line ; from 10 a.m. till 2 grs. every 2 hours.	every hour of Thalline ; the night, 2 grs. every 2 hours.	from 8 a.m. till 7 p.m. 2 grs. every hour ; during the night 1½ grs. every 2 hours.

5. Lammert, baker's apprentice, aged 20, admitted on September 8th. Diagnosis: Typhoid fever, 4th day. Typhoid motions, strong Diazoreaction, raspberry tongue. Initial temperature, rising to 103·8°F on the first two days. The treatment with Thalline begins on the 7th day; on the 10th day the temperature only once shows more than 102·2°F.; on the 11th and 12th day it nearly becomes normal (maximum, 100·9); on the 13th day, decided Apyrexia. Diazoreaction lasts for fully 30 hours after Defervescence.

## September.

	9.	10.	11.	12.	13.	14.	15.	16.	17.
	5th	6th	7th	8th	9th	10th	11th	12th	13th
	day.	day.	day.	day.	day.	day.	day.	day.	day.
8 am.	—	103·8	102·4	99·8	101·5	100·5	98·8	98·4	96·3
10 „	—	103·1	102·6	100·5	101·8	99·4	98·6	97·7	96·4
12 „	—	103·1	102·6	101·8	101·1	99·6	98·0	98·0	97·5
2 p.m.	—	102·2	101·8	102·0	101·1	99·6	99·8	98·8	99·2
4 „	103·7	102·9	102·7	102·4	100·5	100·2	99·8	99·6	
6 „	103·7	102·6	102·4	103·5	101·8	102·9	100·3	100·9	100·2
8 „	103·3	102·9	102·0	103·3	103·3	101·5	100·7	100·9	99·4

$1\frac{1}{2}$  grs. 2 grs. from 9 every hour  $2\frac{1}{2}$  grs. of Thalline.  
 every a.m.  
 hour; hour; every  
 from 1 from 5 hour,  
 p.m. p.m.  $2\frac{1}{2}$  grs.  
 every every  
 hour, hour,  
 $1\frac{1}{2}$  grs.;  $2\frac{1}{2}$  grs.  
 from 5  
 p.m.  
 every  
 hour,  
 2 grains

During the night 3 grs. of Thalline every 2 hours.

6. Anders, coachman. aged 22, admitted on Sep. 4th. Diagnosis: Typhoid fever, 8th day. Enlargement of spleen, Diazo-reaction, Typhoid motion. Thalline administered on 2nd day after admission, remittent character of the fever, total Apyrexia on 14th day. Diazo-reaction until this period. Good results.

## September.

	5.	6.	7.	8.	9.	10.
	9th day.	10th day.	11th day.	12th day.	13th day.	14th day.
8 a.m.	100·3	102·4	97·5	97·3	98·2	97·5
10 „	100·7	102·4	98·4	97·3	97·8	97·5
12 „	101·6	99·6	98·8	98·6	98·9	97·7
2 p.m.	102·7	97·7	99·4	99·6	100·0	96·8
4 „	103·8	101·5	100·0	99·6	100·3	98·8
6 „	103·1	102·2	101·1	100·5	100·9	98·8
8 „	102·6	101·8	101·8	101·3	102·2	97·7

during the night 2 grs. every 2 hours.  
 every hour  $1\frac{1}{2}$  grs.  
 During the night, 2 grs. every 2 hours.  
 the same.  
 the same.  
 from 8 a.m. till 12 a.m.  $1\frac{1}{2}$  grs. every hour; from 12 a.m.  $1\frac{1}{2}$  grs. every hour; during the night, 2 grs. every 2 hours.  
 2 grs. every hour; during the night, 2 grs. every 2 hours.

7. Thomas, coachman, aged 23, admitted on Aug. 28th. Typhoid Fever, 9th day. Initial temperature between 103·1° F. and 104·3° F. Enlarged spleen, Diarrhœa, Bronchitis, Diazo-reaction. After 3 days treatment with Thalline, on 17th day complete and definite Apyrexia.

August.				September.			
	31. 7th day.	1. 8th day.	2. 9th day.	3. 10th day.	4. 11th day.	5. 12th day.	6. 13th day.
6 a.m.	—	—	100·3	—	—	—	From this day normal temperature On Sep. 7th, Thalline was dis-continued.
7 "	—	—	100·7	—	—	—	
8 "	—	100·5	99·8	98·8	98·6	97·5	
9 "	—	—	100·0	97·0	99·6	97·3	
10 "	—	100·5	98·8	98·0	99·8	96·8	
11 "	—	—	99·0	98·0	100·2	97·5	
12 "	—	100·3	99·6	96·8	101·1	97·3	
1 p.m.	—	99·2	98·8	99·4	101·1	97·7	
2 "	—	99·4	100·7	100·2	100·9	98·6	
3 "	—	101·5	101·1	99·8	100·7	98·6	
4 "	—	103·1	100·5	101·1	101·5	99·2	
5 "	—	102·9	101·5	101·8	101·3	98·8	
6 "	104·3	103·3	101·8	102·0	100·7	98·6	
7 "	104·0	102·6	102·2	101·5	101·5	100·0	
8 "	101·3	103·1	102·7	101·6	101·3	99·0	
				from 6.30 a.m. until 7.30 p.m.	from 8.0 a.m. until 2 p.m.	every hour 1½ grs.; during night time as on 3rd day	every hour 1½ grs.; during night time 2 grs. every 2 hours
				every hour 1½ grs.; from 9 p.m. until 7 a.m.	every hour 1 gr.; from 7 a.m. then 1½ grs. every 2 hours.	1½ grs.; during night time as on 2nd day.	

At mid-day 15 grs. of Quinine.

8. Raddatz, workwoman, aged 16, admitted on Sep. 21st, 1885. Typhoid Fever, 15th day. Enlarged spleen, Roseola, strong Diazo-reaction, Pneumonia lob. sin., strong sensorial affection and difficulty of hearing. Serious case. Initial temperature between 102·2° F. and 104° F; prompt antipyretic action of Thalline; after 5 days treatment complete Apyrexia. On the 22nd day enlargement of the Spleen and Diazo-reaction, as well as Diarrhœa still clearly to be traced; the pneumonic infiltration still existing. Irregular increase of temperature during convalescence. Later on relapse in consequence of an error of diet.

**Professor Dr. E. Maragliano, Director of the  
Clinical Institute at Genoa,**

in his special researches on the biologic and therapeutic action of Thalline (*vide* Zeitschrift für klinische medicin, 10th vol., 5th and 8th fascicle, Berlin, 1886, published by August Hirschwald), arrives at the following conclusions :

The results, obtained by numerous observations, with regard to the action of Thalline on the pathological temperature, may be summed up as follows :

1. A single dose of  $1\frac{1}{2}$  grs. may cause a reduction of temperature, amounting from  $1.2^{\circ}$  F. to  $3.6^{\circ}$  F.

2. A dose of 4 grs. may reduce the temperature by  $5.5^{\circ}$  F.

3. Under the influence of 8 grs. the decrease amounts to  $6^{\circ}$  F.

4. After giving 12 grs. it will show  $6.5^{\circ}$  F.

5. Lastly, under the influence of 15 grs. the maximum decrease can amount to  $8.4^{\circ}$  F.

6. The antipyretic effect usually commences 1 hour after administering Thalline, reaching its acme in 2 hours in the case of the decrease being less than  $1.8^{\circ}$  F., and in 3 to 4 hours if amounting to more.

7. After a dose of  $1\frac{1}{2}$  grs. the action lasts from 2—4 hours ; after 4 grs. from 2—9 hours ; after 8 grs. from 2—10 hours.

8. One and the same dose of the remedy does not always show the same intensity of action, the latter depending on the following circumstances :

(a) On the initial temperature : the higher it proves, the more important will be the antipyretic effect of Thalline.

- (b) On the hour of the day ; no definite rule may however be laid down regarding this point. Perhaps the difference in the action is due to the variations of the thermic resistance during day time, and to other reasons unknown to us.
- (c) On the individual susceptibility.

9. If several consecutive doses are given in such a manner that the subsequent dose is administered before the action of the foregoing one has become exhausted, their combined antipyretic effects are shown in a cumulative form.

Furthermore, Professor Dr. E. Maragliano writes :

“ At last I have tried to compare the action of Thalline with that of Antipyrine in one and the same case. I noticed, that after giving the same dose, the action of Thalline is far superior to that of Antipyrine. A dose of 4 grs. of Thalline has the same effect as 15 grs. of Antipyrine. With regard to its duration, however, I could not find any remarkable difference. When considering the dose which is required to keep a patient for a certain time in a state of Apyrexia, my experiments have shown that twice or even three times as much Antipyrine must be administered in order to obtain the same therapeutic effect. As far as I could convince myself, Thalline constitutes the most active of all antipyretic agents in our possession. I usually give Thalline as a powder (in wafers); it may, however, also be administered hypodermically, as it does not produce any local symptoms. Given as an enema, it also acts in an efficacious manner.”

Wm Pickhardt & Kuitroff,  
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## Thalline.

Dr. Henri Desplats, Professeur de clinique médicale à la Faculté libre de Médecine de Lille, Médecin de l'hôpital de la Charité,  
in his interesting pamphlet entitled:

### Utilité de la Médication Antipyrétique

Lille, au bureau du Journal des sciences médicales, 56 rue  
du Port, 1886,

says with regard to Thalline:

„Si je ne partage pas l'opinion du professeur Jaccoud au sujet des dangers de l'antipyrèse, je suis entièrement de son avis lorsqu'il affirme que, de tous les antithermiques, la thalline est le plus efficace à faible dose. C'est en effet aux doses de 0,20 et 0,25 que la thalline est active; aussi n'est-il pas surprenant que Jaccoud ayant au début de ses expériences, administré 1 gr. en une fois à un de ses malades, ait vu sa température s'abaisser graduellement jusqu'à 32°5. J'ai obtenu, pour mon compte, des effets sensibles avec 10 et 15 centigrammes.

L'administration est des plus faciles. Elle se fait en solution dans un liquide quelconque, ou dans un pain à chanter qu'on fait immédiatement suivre d'une petite quantité de boisson pour dissoudre. Les effets locaux sont nuls ou presque nuls, et c'est à peine si j'ai noté deux ou trois fois quelques nausées. Comme avec les autres antipyrétiques, il y a d'abondantes sueurs que rien ne peut prévenir, sauf la diminution des doses <sup>1)</sup>.

Je l'ai administrée à des typhiques, à des varioleux, à des phthisiques, à des pneumoniques, etc., et toujours avec les meilleurs effets. Je ne crains donc pas d'en conseiller l'emploi, malgré les anathèmes un peu légèrement portés contre elle.

<sup>1)</sup> J'ai cependant observé plusieurs fois et j'observe en ce moment un malade atteint d'érysipèle de la face et du cuir chevelu, chez lesquels l'abaissement de la température s'est produit sans sueurs.

On a dit, en effet, s'appuyant sur des expériences bien peu probantes, — et, depuis, cela a été répété, — que, tandis que d'autres antipyrétique modèrent la température en agissant sur le système nerveux, la thalline diminue le pouvoir respiratoire du sang en dissolvant l'hémoglobine. Ce fait est loin d'être prouvé et il me faudra, pour l'admettre, autre chose que les affirmations produites, dans une note récente, à la Société de biologie. Si je m'en rapporte à l'expérience clinique, qui est jusqu'ici notre meilleur guide, je puis dire que la thalline est bien tolérée et que des malades ont pu prendre, sans en éprouver aucun inconvénient, deux paquets de 20 centigrammes par jour pendant une et deux semaines."

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## September.

	21	22	23	24	25	26	27	28
	15 day.	16 day.	17 day.	18 day.	19 day.	20 day.	21 day.	22 day.
8 a.m.	—	102·4	98·6	102·9	104·3	97·1	100	100
9 "	—	—	97·7	—	101·3	96·8	101·3	98·9
10 "	—	102·9	97·7	101·8	98	96·3	98·9	98·2
11 "	—	—	96·8	—	98	97	99·4	97·1
12 "	—	104	98·9	97·8	97·1	98·9	100	97
1 p.m.	—	—	99·8	97·1	96·8	100	99·4	97·3
2 "	—	103·8	100·3	98·6	95	102·7	99·4	97·8
3 "	—	—	98·9	100·7	97·8	102·2	99·4	97·8
4 "	—	103·7	100·3	102·7	99·8	102·9	100·2	99
5 "	—	—	103·1	102·6	101·5	102·9	102	99·4
6 "	—	104	101·3	102·2	101·6	102·7	101·3	99·6
7 "	—	—	102	102·6	102·9	103·3	102·2	100
8 "	103·5	100·3	102·2	101·8	103·5	104	103·5	—
			from 8 a.m. until 10 a.m. 1½ grs; from 10 a.m. until 12 a.m. 1 gr.; from 1 p.m. until 2 p.m. 1½ grs., from 3 p.m. until 8 p.m. every 1½ grs., during night- time every 2 hours	from 8 a.m. until 4 p.m. every hour 1½ grs.; from 4 p.m. until 8 p.m. every hour 1 gr., during night- time 1½ grs. during night- time every 2 hours	from 8 a.m. until 11 a.m. 1½ grs.; from 12 a.m. until 1½ grs.; from 12 a.m. until 8 p.m. every hour 1 gr., during night- time every 2 hours	1 gr. every hour; during night-time 1½ grs. every 2 hours.		

9. Mielentz, apprentice, aged 17, admitted on Sept. 6th. Typhoid fever, 8th day. Roseola, enlarged spleen, Diazoreaction, diarrhoea, strong parenchymatose swelling of the tongue accompanied by ulceration. Serious Case. Exquisite antipyretic action of Thalline after 2 days treatment, which was resorted to on the 12th day, temperature exceeding 102·2°, F. was only registered once a day; on the 18th, after 8 days treatment with Thalline, Apyrexia was nearly complete. On the two following days there was still fever of a remittent type. From the 21st day the temperature was normal. Later on, on the 30th day relapse, ending in death. We think, that in this case, showing according to the general character a very serious instance of typhoid fever, the continuous treatment with Thalline had been instrumental in diminishing the duration of the Typhoid fever, there being Apyrexia on the 20th day, the intensity of the symptoms indicating a duration of at least 4 weeks.



10. Paul, aged 19, bootmaker's apprentice, admitted on June 29th. Typhoid fever, 12th day. Enlarged spleen, Diazoreaction. The Thalline treatment was resorted to on the 15th day, single doses being given up to 15 grs., and, nevertheless, only transient Apyrexia attained. From the 21st day continuous use of  $1\frac{1}{2}$  grs. every hour, resulting in well-defined Antipyresis of a progressive form; after three more days complete Apyrexia; good results. The powerful action of small and frequent doses is shown in a remarkable manner by the temperature curve, when compared with large single doses (principally on July 7th).

July 7 16th day.	July 8 17th day.	July 9 18th day.	July 10 19th day.
8 a.m. 100.9	8 a.m. 102.4	100.9	99.6
10 „ 101.6	9 „ 101.3	99.8	99
12 „ 101.3	10 „ 100.3	99.2	98.8
1 p.m. 99	11 „ 100	98.4	98.2
2 „ 97.8	12 „ 100.3	99.2	97.8
3 „ 96.8	1 p.m. 100.7	100.3	98.2
4 „ 97.8	2 „ 99.8	98.6	99.4
5 „ 102.2	3 „ 100.3	99.6	99.8
	4 „ 99.6	99.4	97.8
	5 „ 99.4	98.9	98.8
	6 „ 102.4	101.3	—
	7 „ 102.9	102.4	99.4
	8 „ 102.4	102.6	102.2
At 12 a.m., 15 grs. of Thalline, no shivering; at 2 p.m., intense sweating.	From 8 a.m. until 5 p.m., $1\frac{1}{2}$ grs. of Thalline every hour.	At 8 a.m. free perspiration; from 8 a.m. until 5 p.m., $1\frac{1}{2}$ grs. of Thalline every hour; at 1 p.m. sweating.	From 8 a.m. until 5 p.m. $1\frac{1}{2}$ grs. of Thalline every hour. No sweating; no shivering,
July 11 (20th day).			
8 a.m. 100.9			
9 „ 98.8			
10 „ 97.7			
11 „ 97.1			
12 „ 97.3			
1 p.m. 98			
2 „ 97.8			
3 „ 99.2			
4 „ 98.9			
5 „ 98.6			
6 „ 99.4			
7 „ 99.4			
8 „ 99.4			
From 8 a.m. until 7 p.m., $1\frac{1}{2}$ grs. of Thalline every hour; moderate sweating; no shivering.			

11. Oppé, aged 19, porter, admitted on July 8th, 1885. Diagnosis: Pneumonia, during convalescence Typhoid fever,

against which at first Quinine was given. On the 15th day, in the period of remission (Temp. 98·6° F.—102·6° F.), continuous doses of Thalline were administered. After one day's treatment, definite Apyrexia. Good result.

## September.

	1 14th day.	2 15th day.	3 16th day.	4 17th day.
8 a.m.	99·6	98·6	96·8	97·7
10 „	100·7	98·2	97·3	97·5
12 „	100·7	98·6	98·6	98·4
2 p.m.	100·3	98·6	100	99
4 „	101·5	100	98·2	98
6 „	102·2	100·9	100	98·9
8 „	102·6	100·9	7 p.m. 100·5	99
		$\frac{3}{4}$ grs. every hour ; during night- time $1\frac{1}{2}$ grs. every 2 hours, from 9 p.m. until 7 a.m.	From 8 a.m. until 2 p.m. 1 gr. of Thal- line every hour ; from 2 p.m. until 8 p.m. $1\frac{1}{2}$ grs.	From 8 a.m. until 4 p.m. every hour, $1\frac{1}{2}$ grs. of Thalline.

During night time  $1\frac{1}{2}$  grs.  
of Thalline.

12. Meyer, servant-maid, aged 30, admitted on August 24th. Typhoid fever, 7th day ; enlarged spleen, Roseola, Diazoreaction, typhoid stool, bronchitis, tongue dry and chapped. Treatment at first with cold bathing, afterwards with Quinine, until the 16th day. On the 17th day, in the period of remission (99·4° F—102·7° F) Thalline was given ; critical decrease of the fever on the same day. Good result.

## September.

	2 16th day.	3 17th day.	4 18th day.	5 19th day.
8 a.m.	99·6	8 a.m. 100·9	8 a.m. 98·2	8 a.m. 96·8
10 „	99	9 „ 103·1	9 „ 98·2	9 „ 96·8
12 „	99·4	10 „ 102·9	10 „ 97·7	10 „ 96·8
2 p.m.	102·4	11 „ 101·3	12 „ 100	12 „ 96·8
4 „	102·2	12 „ 102·9	2 p.m. 97·1	2 p.m. 97·3
6 „	103·1	1 p.m. 100·3	4 „ 97·5	4 „ 97·3
		2 „ 102·2	6 „ 98·6	6 „ 97·3
		3 „ 100·7	8 „ 98·2	8 „ 98·6
		4 „ 100·5		
		5 „ 99·8		
		6 „ 98		
		1 gr. of Thalline every hour ; during night time, $1\frac{1}{2}$ grs. every 2 hours.	$1\frac{1}{2}$ grs. every hour ; during night time, $1\frac{1}{2}$ grs. every 2 hours.	From 11 a.m. until 5 p.m., $1\frac{1}{2}$ grs. ; from 5 p.m., $\frac{3}{4}$ grs. ; during night- time, $1\frac{1}{2}$ grs. every 2 hours.

At midday, 15 grs. of Quinine.

13. Schmidt, servant-maid, aged 18, admitted on Aug. 24th. Light case of typhoid fever of 13 days duration; after 8 days, relapse, in consequence of an error of diet; from the 2nd day in the relapse Thalline was given in doses of  $1\frac{1}{2}$ — $1\frac{1}{2}$  grs. every hour without apparent effect; undulating fever curve following a dose of  $2\frac{1}{2}$  grs.; fever ceased on the 6th day of relapse, after 3 days treatment; on subsequent 3 days nocturnal increase of temperature of intermittent character; definite Apyrexia on 10th day of relapse. The antipyretic effect of larger doses of Thalline is clearly shown in the scale of temperature, becoming very striking on the 6th day, when doses of 3 grs. were given every hour.

### September.

	7 21st day.	8 22nd day.	9 23rd day.	10 24th day.	11 25th day.	12 26th day.	13 27th day.	14 28th day.
8 a.m.	100.5	101.1	102.6	102.7	100.7	100.2	100.9	98.6
9 "	—	102.7	100.5	—	—	100.7	100.2	98.2
10 "	102.2	101.8	102.2	103.7	101.8	99	98.9	97.8
11 "	—	102.2	102.4	—	—	98.9	99.6	97.1
12 "	102.6	101.6	102.6	99.6	100.2	98.2	98.6	97.5
1 p.m.	—	102.4	103.7	—	—	99.6	98.2	97.8
2 "	103.3	99	101.8	100.9	101.3	100	98.6	99.4
3 "	—	99.4	102.6	—	—	100.7	100	101.1
4 "	102.6	100.5	102.6	103.7	100.7	99.6	99.6	100.7
5 "	—	101.3	102.9	—	—	100.2	99.4	100.2
6 "	102.9	103.1	103.3	101.5	100	100.9	99.2	99.2
7 "	—	100.5	103.1	—	—	102.7	103.1	99
8 "	102.6	102.2	102.9	100.9	98.6	103.7	101.8	99
	During night time 2 grs. of Thalline.	In the morn- ing, every hour; from 11 a.m., $1\frac{1}{2}$ grs. every hour; during night time, $1\frac{1}{2}$ grs. every 2 hours.	$1\frac{1}{2}$ grs. every hour.	From 9 a.m. every hour, $2\frac{1}{2}$ grs.; in the afternoon, wards, every 2 hours alter- nately, $1\frac{1}{2}$ grs. and 3 grs. of Thalline.	From 9 a.m. until 11.30 a.m. $1\frac{1}{2}$ grs.; after- noon, wards, every hour.	2 grs. every hour.	2 grs. every hour.	
							During night time, 3 grs. every 2 hours.	

On the succeeding days, normal temperature.

On September 15th, 16th, 17th, every hour, 2 grs.

" " 18th, every hour,  $1\frac{1}{2}$  grs.

" " 19th and 20th, every 2 hours,  $1\frac{1}{2}$  grs.

" " 21st Thalline was discontinued.

No Thalline during  
the night.

The 13 cases referred to comprise nine patients, to whom Thalline was given immediately after admission into the Hospital and mostly at the end of the first and not later than the end of the second week. The results attained are highly satisfactory, inasmuch as Apyrexia was apparent on the average

after 4—5 day's treatment with Thalline. Even the two severe cases (Mielentz and Raddatz) did not require more than 5—8 days treatment. The three following cases have reference to patients, to whom Thalline was given only later on, after previous treatment with other therapeutic agents, such as Quinine, with cold bathing, etc., etc., *i.e.* in the period of remission. In these cases also complete Apyrexia set in after 1—2 day's treatment with Thalline. In the last case a fresh relapse was treated with Thalline from the beginning. The effective and individually large dose of 3 grs. every hour was given only from the 6th day, thus definitely stopping the febris continua, inasmuch as on the following two days there were only nocturnal exacerbations of temperature of an intermittent type.

We further add two cases of a refractory nature, showing no results whatsoever from the treatment with Thalline. In one of them (Gaedke) there was exacerbation of the fever in the midst of a state of remission due to the action of Thalline, and probably caused by a recrudescence of the typhoid process. The other case proved altogether and completely refractory against Thalline.

Lastly we have given Thalline to 4 patients at the end of typhoid fever of a protracted type (5th and 6th week) and could not convince ourselves of any action whatever. This seemed the more surprising, as all 4 cases showed a febris remittens with small maximal temperature (the highest being 102.2°F). Hence, according to our experience, methodical treatment with Thalline will be found inadmissible in cases of a protracted nature. Whether larger single doses would have more effect in such instances, remains to be seen by further special investigations,—to us however this appears rather improbable.

14. Boehnke, tailor, aged 21, admitted on July 6th. Typhoid fever, 9th day; enlarged spleen, Roseola, typhoid stools, Diazoreaction. Thalline on the 13th day. Single doses were followed by disagreeable concomitant symptoms. Continuous treatment with Thalline was resorted to on the 19th day, and continued for seven days, without showing any progressive antipyretic effect, stronger remission being apparent only temporarily. Thalline therefore was discontinued and 8 grs. of Quinine given three times daily. Apyrexia after 2 days. Thus there was complete want of any favourable action regarding either Apyrexia or the shortening of the duration of the illness; on the contrary we may almost have the impression

that Thalline acted in a manner favouring the access of fever, if we consider that Apyrexia set in immediately after discontinuing Thalline and substituting Quinine.

## July.

	16 18th day.	18 20th day.	20 22nd day.	22 24th day.	23 25th day.	24 26th day.	25 27th day.
8 a.m.	101.5	104.3	102.9	101.8	101.6	100	98.6
9 "	99.4	102.9	100.7	100.9	96.3	...	...
10 "	97.5	100.9	99	98.6	96.3	99.6	98.2
11 "	97.1	99.4	98.4	96.8	97.8	...	...
12 "	95	99.4	100.2	99.8	97.8	100.2	96.8
1 p.m.	95.9	102.7	99.4	100	97.8	...	...
2 "	95.9	103.5	100.2	100.5	102.2	100	99
3 "	97.7	103.3	101.6	102	102.7	...	...
4 "	99.4	100.7	101.3	102.7	103.3	101.3	99
5 "	101.5	102	102.6	103.1	102.9	...	...
6 "	104.9	102.2	102.6	102.9	102.7	101.6	99
7 "	103.3	102	103.1	102.2	102.7	...	...
8 "	102.6	...	...	102.9	102.6	98.6	98.2
9 "	100.7	...	...	...	...	...	...
	from 8 a.m. until 10.30 a.m.	from 9.30 a.m. until 11 a.m. $\frac{5}{8}$ grs. every half- hour; from 10.30 a.m. until 2.30 p.m. $1\frac{1}{2}$ grs. every half- hour; from 2.30 p.m. until 4 p.m. shiver- ing.	at 8 a.m. sweat- ing; from 8 a.m. until 8 p.m. $\frac{3}{4}$ grs. every half- hour; from 11 a.m. until hour; no $\frac{1}{2}$ gr. every half- hour; no shiver- ing, no sweat- ing.	from 8 a.m. until 5.30 p.m. $\frac{3}{4}$ grs. every half- hour.	from 8 a.m. until 10 a.m. $\frac{3}{4}$ grs. every half- hour; after that 8 grs. of Quinine three times daily.	8 grs. of Quinine three times daily.	

15. Gaedke, bakers' apprentice, aged 20, admitted on Sep. 10th, (4th day). Enlargement of spleen, strong Diazoreaction, Bronchitis and Glossitis. Temperature on 6th day almost constantly 104°F.; from 7th day Thalline given in progressively rising doses up to  $2\frac{3}{4}$  grs. every hour until the 13th day, on which a febris remittens was noticeable. On the 14th day, although the same dose was administered, the temperature rose on the average 1.6°F., and consequently the medication with Thalline was discontinued. Apyrexia on the 25th day.

## September.

	19 13th day.	20 14th day.
8 a.m.	99·2	100·5
10 „	99·2	101·1
12 „	96	100·2
2 p.m.	102	101·3
4 „	102·9	101·8
	at 5 p.m. Thalline discontinued.	
6 „	101·8	104·6
2½ grs. of Thalline every hour; during night-time 3 grs. every 2 hours.		

16. Jaap, hall porter, aged 34, admitted on Sept. 14th, Typhoid fever of a lentescient type; patient seeks admission into the Charité only on the 30th day. On the 36th day treatment with Thalline in the period of remission (100 to 102·2° F.) After 7 days treatment the febris remittens still prevalent (reaching 102° F.), decreasing however from this time slowly during several days.

17. Baerwinkel, labourer, aged 33, admitted on August 1st. Typhoid fever, 8th day. At the end of a slow fever, against which Quinine was given continually, Thalline is administered on the 44th day at a period marked by a slightly remittent fever with nocturnal temperature up to 100·9° F. A four days' treatment with Thalline (1 gr. every hour) is without the slightest effect. Two days after stopping the drug there is definite Apyrexia on the 49th day.

18. Bartsch, butcher's apprentice, aged 36. At the end of the 5th week of a severe typhoid fever of lentescient type with temperature of 100·3 to 102·6° F., Thalline is given on the 34th day for 5 days together without modifying the fever in the least; 3 days afterwards Apyrexia.

19. Scholz, attendant at the Charité, aged 22, admitted on August 21st. Lentescient typhoid fever, 11th day. At the end of the 6th week Thalline is given, the fever showing a moderately remittent type (100 to 101·8° F.); after 6 days' treatment complete Apyrexia, which would certainly have taken place as well without any medication whatever.

After thus enumerating the cases observed by us, in short outlines, we must now, although it may be considered rather late, undertake to solve the preliminary question as to the quantity of Thalline to be used and the best manner of its application; this point being of paramount importance as regards a successful continuation of the treatment.

The reaction of feverish patients against the use of Thalline will always be influenced to a certain degree by the Genus morbi,

phthisical patients showing altogether a more rapid and more energetic reaction against Thalline and the Antipyretics in general when compared with patients suffering from severe pneumonia and typhoid fever. Apart from this, one and the same kind of illness is apt to show an extraordinary difference as regards the action of this remedy ; a difference, based not only on the intensity of the morbid process but on a multitude of individual and therefore unaccountable conditions. The mode of Thalline treatment selected by us, is also subject to such purely individual circumstances, the hourly doses varying accordingly—as may be seen from the cases—in wide ranges from  $\frac{2}{3}$  to  $1\frac{1}{2}$  and even 3 grains.\*

The principal question regarding the treatment of typhoid fever with Thalline is to determine by systematical investigation the individual dose, this mode alone guaranteeing a satisfactory result in the respective case, inasmuch as too small a quantity is unattended by any corresponding effect, while on the other hand too large a dose is sure to be accompanied by troublesome and even unbearable symptoms. In fixing the quantity required for each separate case we shall be rewarded for our little trouble by being able to continue the same dose for many days and even weeks together, without fear of any disagreeable concomitant symptoms. Which now is the dose required for each individual case ? It is the quantity, sufficient to exercise a perceptible action at the beginning of the treatment and during its continuous administration in reducing the temperature in a decisive although not very important degree, causing for instance in a case of continued fever of  $103.1^{\circ}\text{F.}$ , a decrease amounting to  $100.3\text{--}101.3^{\circ}\text{F.}$  for several hours. In order to fix the effective minimum quantity to be used, the treatment may be best begun with a dose  $\frac{2}{3}$  to 1 gr. every hour, increasing it gradually in intervals of 2–3 hours, under constant thermometrical control, to such a degree as will clearly show the above-mentioned influence on the temperature.

The further development of the fever curve, as well as the appearance of the phenomena soon to be described, will show whether the dose selected is the proper one, thus giving an opportunity of correcting it easily in one or the other direction. Should there be a stronger resistance against Thalline in some

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\*Concerning these matters the kind of Thalline Salt is also of importance, Sulphate of Thalline containing 77 per cent., Tartrate 52 per cent., Tannate only 33 per cent., of the actual base. The latter preparation, manufactured at our instigation, may be principally indicated, on account of its difficulty of solution and its large quantity of Tannic Acid, in cases of typhoid fever, especially when accompanied by profuse evacuations.

cases, this will soon become evident by the absence of all reaction, (such as variation of temperature, sweating, &c.,) and consequently without further loss of time, the dose may be increased by  $\frac{1}{4}$ — $\frac{1}{2}$  gr., in order to shorten the preliminary period. Having definitively fixed the individual dose of Thalline by investigations of this kind, it will be found advisable to continue the same—best in the form of pills—for every hour in daytime and every two hours during the night. In administering continuous doses of Thalline in a fresh case of typhoid fever the following changes of temperature will be observable, as shown by careful measurement during the greater part of the day, appearing at the same time genetically connected and verging one into another.

The first period is marked by a fever curve, showing a decrease of temperature, occurring rather frequently, lasting only a short time and being relatively unimportant, when compared with the constant high temperature of the febris continua. Hence the curve, with regard to the steadiness of the temperature, will present an undulating character, at the same time showing no difference from the initial period with regard to its maximum height.\*

The second Thalline period exhibits a totally different curve. There is a temporary antipyretic decrease during several hours of the day, especially in the forenoon, the febrile temperature of the first morning hours descending gradually to the normal state, remaining so for a short time, and rising again gradually to its previous maximum.

The third period is more in conformity with the well known febris remittens, evincing however a certain peculiarity, inasmuch as the rising curve frequently shows an indented course, the nocturnal maximum decreasing again during the succeeding hours.

The fourth period, called the period of the "highly indented curve," is a sequel of the three foregoing ones, showing complete Apyrexia in daytime, interrupted only by a strong and rapid increase of temperature, reaching  $102\cdot2$ — $103\cdot1^{\circ}$  F., of one to two hours' duration. Its appearance is usually accompanied by a sensation of slight shivering. According to our observations the appearance of the fourth period denotes that the patient has entered the convalescent state.

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\*The discontinuous influence on the temperature, notwithstanding the constant administration of the Antipyretic, may be best explained by the statement of Filehne, that the feverish (over-heated) nervous system is acted upon by the synthetic alcaloids; the drug losing its specific virtues by and during its action in producing Apyrexia, so that the constantly active pyrogene agent becomes enabled again to assert its primitive power.

It seems hardly necessary to point out, that according to the individuality of each separate case, one or the other fever-period may be developed in a smaller degree or even completely obliterated, and that Thalline when administered at a later period of a respective case, will at once initiate the 3rd state of remittent fever.

On the other hand it may be stated as a fundamental law, that in treating a fresh case of typhoid fever with a dose properly adapted to the individual circumstances, the fever periods will constantly succeed each other in the manner indicated above, thus informing us already during the first days of Thalline treatment to a certain degree which phase of the morbid process we have to deal with, and whether the fever in the respective case has reached its acme or is already on its decline. An exact definition of the duration of the single fever periods can only be given on the basis of more numerous researches, on account of the great variety of the typhoid process.

As will be seen from the cases above related, the results of Thalline treatment in typhoid fever have proved highly satisfactory, this being evident principally in the first group of fresh cases, showing in their majority an unusually rapid Apyrexia, after 3—5 days' treatment with Thalline; an Apyrexia contrasting strongly with the totality of the prevalent symptoms and the presumptive estimation of the morbid process, based thereon.

In those cases where the treatment was resorted to in later periods of the typhoid process (about the 2nd or 3rd week) we also had occasion to see some surprisingly good results from the use of Thalline; these were only totally absent in greatly protracted, lentescent forms of typhoid fever. Our observations therefore clearly demonstrate that Thalline, given according to our method, possesses a powerful antipyretic action, thus evidently constituting a judicious antipyretic remedy.

Another question naturally presenting itself, was whether Thalline, apart from its antifebrile properties, may not as well show specific virtues on the morbid process itself. We are well aware of the difficulties encumbering this important matter, and we consider it impossible to form a decided opinion respecting it without awaiting further elaborate researches. At the same time we believe ourselves justified in saying, that, considering the immediate observations derived from the material at our disposal, we are under an impression that Thalline really possesses—besides the antipyretic—some specific properties.

In making this statement we have been guided by the following considerations:—

I. By the typical and progressively increasing influence

on the temperature, as shown in the different fever periods, (compare 2nd and 4th period) and to some extent characteristic of the Thalline curve. Considering the improbability for many reasons of an accumulation of Thalline in the tissues, especially on account of the conditions of elimination, this may be best explained by assuming that, generally speaking, the febrile power is losing its energy under the influence of Thalline, the same dose of this remedy thus successively gaining in efficacy.

II. As a moment of great importance, speaking in favour of an artificially provoked and precipitated Apyrexia and against the assumption of a light and abortive form of typhoid fever, we may cite the persistence in a good many cases of the swelling of the spleen and the continuance of the diarrhoic motions, and particularly the protracted duration of the Diazoreaction after Apyrexia. A certain value is to be attached to the latter circumstance, showing the presence of a conspicuous Diazoreaction ( $\pm$  to  $\pm\pm$ ) in most of our successful cases, extending even into the period of Apyrexia; this condition, according to especial studies, made by one of us consecutively for three years, being contrary to all other observations respecting the reaction in light cases of typhoid fever, which, as stated by him, generally show but a weak and limited area.

III. Another fact deserving notice is demonstrated by the frequent occurrence of an apparently spontaneous, irregular increase of temperature of an indented character during the first days of Apyrexia and notwithstanding the continuous use of Thalline. This usually takes place either at night or early in the morning, and is not to be traced in a similiar manner during the convalescent period of cases of typhoid fever not treated by Thalline, all outward causes productive of fever, such as errors of diet, excitement through visits of friends, etc., being carefully excluded.

We may therefore draw the conclusion from this experience that we had to deal in our cases with a premature Apyrexia produced artificially in typhoid fever of a normal or moderately severe type, and it may consequently be presumed, with all reserve, that Thalline, when properly administered in abdominal Typhoid, may after all exercise a specific action. The absence however of any results worth mentioning in a small minority of fresh cases, as well as in protracted forms of four to six weeks' duration, may perhaps be cited as opposed to the theory of a specific property.

In any case it would appear premature to discuss the question relating to the sphere of the specific nature of drugs,

which, although interesting, is still enveloped in darkness, and the remark may therefore suffice, that the same condition is apparent with regard to salicylic acid, the anti-rheumatic action of which by this time has become positively an axiom. This remedy also refuses to act in a certain percentage of fresh cases, although generally showing the greatest efficacy in the freshest cases; besides, salicylic acid, as is well known, acts principally on the affections of the joints, leaving the other usual complications of the rheumatic process untouched as regards either a curative or a prophylactic effect.

In any case it may be considered advisable to be very careful in convalescent cases showing a rapid Apyrexia after the use of Thalline, and principally to regulate the diet of such patients in an appropriate manner, as it appears impossible for the deep seated anatomical lesions and particularly the intestinal ulcerations to become healed up after a few days time, thus still presenting open channels of infection. In this manner we have met with relapse in two cases, one of them being traceable with certainty to an error of diet. Furthermore it may be considered expedient, according to our therapeutical knowledge, to continue the use of Thalline at least during the first few days after Apyrexia has set in.

Our experience in typhoid fever has induced us to use Thalline also in other ailments, in order to try its curative effects, and considering the close chemical relations existing between Thalline and Quinine, intermittent fever naturally stood in the foreground as an object of investigation. We have given Thalline in two cases of ague, without seeing any antitypical effects, Quinine on the contrary acting immediately in the promptest manner.

In a case of articular Rheumatism, rapidly cured by the use of Salicylic acid, the previous treatment with continuous doses of Thalline had led to no result, so that, according to our experience, further therapeutic trials appear to have no chance of success.

In two other affections, viz : Erysipelas and genuine Pneumonia, we have obtained better results; although restricted with regard to the material at our disposal, we have observed a critical decline of the morbid process, following in the wake of treatment with Thalline, as may be seen from the curves, published in a paper by Dr. Laquer, and consequently further researches with regard to these particular maladies may be urgently recommended.

A paper by Jaccoud (Bulletin de l'académie de médecine, No. 43, page 1443) has just come to our knowledge, containing comparative remarks on Thalline and Antipyrine with regard

to their respective therapeutic effects. Jaccoud, according to his observations, comes to the conclusion, that both these antipyretics possess only a very limited area of operation.

It may be worth mentioning that Jaccoud, apart from these fundamental scruples, prefers the use of Thalline to that of Antipyrine, the doses required of the former being smaller, the concomitant symptoms, such as sweating and shivering less marked as compared with Antipyrine, and the disagreeable Antipyrine-rash, which in cases of severe typhoid fever and of progressive phthisis may assume a dangerous type, being totally absent after treatment with Thalline. The observations made above with regard to the attacks of shivering may be repeated respecting the danger of collapse, and forming as they do a valuable corroboration of our own previous investigations, we think it advisable to quote the respective sentence in his own words :

Les chances du collapsus sont les mêmes avec les deux agents, mais ce danger spécial est plus insidieux avec l'antipyrine. Je m'explique. Pour l'une et l'autre substance cet accident dépend de l'individualité du malade et non pas de la dose : de la mon précepte de tantôt, de n'intervenir au début qu'avec des doses inférieures, afin de tâter l'intolérance. Le précept s'applique à l'antipyrine tout comme à la thalline.

Mais avec la thalline la notion ainsi acquise est une base solide sur laquelle on peut se reposer en tout sécurité ; si l'on a constaté par une première épreuve que l'individu supporte bien sans aucune manifestation de collapsus une dose de 30 centigrammes de thalline par exemple, on peut la répéter sans crainte autant de jours qu'on voudra à supposer, bien entendu que l'élimination urinaire soit correcte.

J'ai cru d'abord qu'il en était de même avec l'antipyrine ; mais un fait que j'ai observé m'a prouvé qu'il n'y a pas à compter sur l'enseignement du premier jour et que le péril renaît avec chaque administration.

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